REMARKS

In accordance with the present invention, methods are provided for treatment of subjects having a disease state mediated by a particular steroid or steroid-like hormone receptor subtype. The invention method comprises administering to such a subject an effective amount of a ligand that selectively interacts with the receptor subtype associated with the disease state being treated, to a significantly greater extent than with other subtypes of the same receptor class. Invention methods provide the unexpected advantage that treatment with a ligand selective for a particular receptor subtype associated with the subject's disease minimizes the occurrence of side effects caused by the activation of hormone responsive pathways not directly associated with the disease state being treated.

Claims 1, 5-8 and 16-18 are currently pending herein, no claims having been amended or new claims added by this Response.

The Rejection under 35 U.S.C. § 103

The rejection of claims 1, 5-8 and 16-18 under 35 U.S.C. § 103 over Crettaz et al. *Biochem. J.*, 272:391-397, 1990 (hereinafter "Crettaz"); Astrom et al. *BBRC,* 173(1):339-245, 1990 (hereinafter "Astrom"); EPA 0170105 (hereinafter "'105"); and EPA 0220118 (hereinafter "'118") is respectfully traversed for the following reasons.

Applicants' invention, as defined by claim 1, provides methods of treating a disease state mediated by a particular steroid or steroid-like hormone receptor subtype in a subject in need thereof. The invention method distinguishes over the references relied upon, taken alone or in combination, by requiring the administration of an effective amount of a ligand which selectively interacts with the steroid or steroid-like hormone responsive receptor subtype associated with the disease state being treated, to a significantly greater extent than with other subtypes of the same receptor. Thus, the subject treated according to the invention method is one having a disease that

is associated with a particular subtype of a member of the steroid/thyroid hormone superfamily of receptors and an important part of the invention method involves selection of a ligand that will most efficaciously treat such a subject.

As acknowledged by the Examiner, the references cited "do not label the compounds as selective ligands" (Office Action, page 2). To overcome this admitted deficiency in the references, the Examiner improperly advances the argument that an inherent mechanism of drug action would allegedly render the claimed treatment method obvious, as follows:

> ...pharmaceutical methods are not limited by the possible mechanism of drug action because all mechanisms inherently occur upon administration of the drug regardless of the label given to the compound.

(Office Action, page 2). The Examiner's improper reliance upon the inherent mechanism of drug action in framing the rejection is further illustrated in the Examiner's unsupported assertion that the compound of claim 16 would "inherently bind to certain receptor subtypes in a selective manner when the compound is administered to patients with skin disorders and cancer as was performed in the Crettaz reference" (Office Action, page 2). Applicants submit that this line of argument is improper under 35 U.S.C. § 103.

According to ***In re Spormann,*** a rejection for alleged obviousness is <u>not</u> properly based upon inherency:

> [The] inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.

150 *USPQ* 449, 452 (C.C.P.A. 1966). Accordingly, Applicants submit that the Examiner's unsupported assertion that particular compounds disclosed by Crettaz, or any of the other references cited herein, would inherently bind with specificity to a particular receptor subtype, does not establish the *prima facie* obviousness of Applicants' method claims. Applicants' invention is based upon the discovery that ligands exist that can select between otherwise very

closely related members of the steroid/thyroid hormone superfamily of receptors. Thus, administration of such a compound to a subject having a disease state associated with the receptor with which the compound selectively interacts affords particular therapeutic advantage, for example by minimizing the occurrence of side effects caused by the activation of hormone responsive pathways not directly associated with the disease state being treated.

Further, Applicants respectfully disagree with the Examiner's assertion (with respect to the compound of claim 16) that Crettaz teaches "the use of such compounds to treat retinoid responsive skin disorders and cancer (page 391, column 1, first paragraph)" (Office Action, page 2). Applicants respectfully submit that Crettaz fails to teach or suggest that specific disease states are responsive to treatment by retinoids that bind with specificity to a particular retinoid receptor subtype, or that unwanted side effects of retinoid treatment can be minimized by selecting a ligand having selective activity that is matched to the cellular mechanism operative in the particular disease state being treated. In fact, Crettaz's statement regarding the therapeutic utility of retinoids (relied upon by the Examiner) refers to synthetic retinoids as a single "class of compounds" having value in the treatment of such various diseases as "dermatological disorders" and "cancer" (Crettaz, page 391, column 1, first paragraph). In this statement Crettaz shows no recognition that different receptor subtypes are involved with the various diseases referred to, much less any suggestion that compounds showing a difference in specificity between receptor subtypes would have utility in the treatment of a subject having a disease state associated with a particular receptor subtype. Thus, Crettaz fails to suggest the invention of claim 1 precisely because Crettaz fails to teach or suggest selecting a specific ligand to use in treatment of a subject having a disease state associated with a particular subtype of a member of the steroid/thyroid hormone superfamily of receptors.

Further reliance on Astrom does not cure the deficiencies of Crettaz. Applicants respectfully disagree with the Examiner's assertion that:

> Astrom teaches compound II, etretin (page 340, "Materials") may be useful as an antitumor and antipsoriatic agent ...

(Office Action, page 2). Astrom's comment regarding efficacy of "retinoids" speaks only in general terms about the efficacy of "retinoids" as a class (Astrom, page 339, first paragraph) and does not identify any diseases associated with any particular receptor subtype. Indeed, Astrom does not even distinguish between the classes of RAR and RXR. Thus, Astrom fails to suggest Applicants' method of treating subjects having a disease associated with a particular retinoid receptor subtype by administration of a retinoid compound that selectively binds to a particular RAR or RXR receptor subtype.

Further reliance on EPA '105 is unable to cure the deficiencies of Crettaz and Astrom, as EPA '105 also fails to disclose or suggest the use of compounds that have the ability to selectively interact with one specific steroid or steroid-like hormone-responsive receptor subtype relative to other subtypes of the same class for the treatment of disease states associated with that particular receptor subtype. Contrary to the Examiner assertion that "105 teaches retinoids for treating leukemia specifically ...and compounds encompassing applicant's compound III for treating malignant diseases" (Office Action mailed April 1, 1998, page 4), '105 fails to disclose which of the many benzoic acid derivatives disclosed therein would be chosen to treat a subject afflicted with mylogenous leukemia or any of the other disorders mentioned therein. Further EPA '105 fails to suggest that the most efficacious way to treat a disease state associated with a particular steroid or steroid-like responsive receptor subtype is to select a ligand that selectively interacts with that particular receptor subtype. Thus EPA '105 fails to suggest treatment of a disease state associated with a particular steroid or steroid-like responsive receptor subtype with a ligand that selectively interacts with that particular receptor subtype, as required by Applicants' claim 1.

Further reliance on EPA '118 is unable to cure the deficiencies of Crettaz, Astrom, and EPA '105. Similar to the other three references relied on, EPA '118 does not disclose or suggest

the use of compounds that have the ability to selectively interact with one specific steroid or steroid-like responsive receptor subtype (e.g., RARα v RARβ), relative to other retinoid responsive receptor subtypes, to treat a subject having a disease state associated with a particular receptor subtype.

As neither Crettaz, Astrom, EPA '105, nor EPA '118 discloses or suggests the use of ligands that are selective for specific steroid or steroid-like hormone-responsive receptor subtypes in a patient having a disease state associated with such a particular steroid or steroid-like responsive receptor subtype, the combination of references relied upon does not disclose or suggest Applicants' claimed method. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

In view of the above remarks, reconsideration and favorable action on claims 1, 5-8 and 16-18 are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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